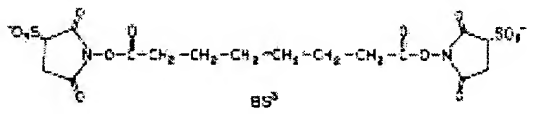
REMARKS

Declaration under 35 USC §1.132

In response to the October 14, 2003 Advisory Action in the above-identified application, applicants submit herewith a Declaration by Dr. Anthony DeVico. In the enclosed Declaration (Appendix A) Dr. DeVico describes test results that clearly demonstrate that an amino acid spacer positioned between a virus coat polypeptide and viral receptor polypeptide, as in the claimed chimeras of the present invention, is not the equivalent of a chemical crosslinker that covalently binds two peptides together.

Dr. DeVico states that, as a co-inventor of the present application and cited references U.S. Patent Nos. 5,518,723 and 5,843,454, steps were taken in the complexes of the cited references to permanently bond the virus coat polypeptide and viral receptor polypeptide with a bivalent cross-linking agent that covalently linked them together. He further describes that the crosslinking agent, bis-sulfosuccinimidyl suberate, a homobifunctional cross-linking reagent with amine reactivity having a structure as set forth below:



was used to obtain the crosslinked complex. This crosslinking agent forms a complex that is not a single chain polypeptide wherein the spacer forms peptide bonds between the terminal α-amino group of one protein and the terminal α-carboxyl group of protein. Instead the crosslinking agent binds only to primary amines on the respective proteins, and as such, the complex is entirely different from the chimeras of the presently claimed invention because the end product is not a single chain polypeptide.

Dr. DeVico further provides and discusses test results that show that the use of the covalent crosslinker occludes epitopes on BaLgp120/sCD4 complexes, however these epitopes are exposed on the full length single chain (FLSC) chimeras of the presently claimed invention. Thus, the covalently crosslinked complexes of DeVico '723 and '454 are not the equivalent of the FLSC of present invention. Specifically, the test results show that the structure of the BaLgp120/sCD4 complex reduces the antigenicity of the 39F, C11, A32 and 17b epitopes by essentially occluding these

epitopes. In contrast, all of these epitopes were exposed on the chimeras of the presently claimed invention. Thus, the covalent crosslinker alters the antigenic site and the use of a chemical crosslinker is not the equivalent to the amino acid spacer of the present invention. In fact, the FLSC polypeptide of the present invention provides for a far superior complex that can be used to potentially block HIV-1 via its coreceptor CCR5. Further, the FLSC polypeptide can be used to screen for reagents that may potentially block HIV-1 via its coreceptor CCR5.

Dr. DeVico describes that the complexes of both DeVico '723 and '454 are fused together by a covalent bond formed by a chemical crosslinker and further states that a covalent bond does not naturally occur when you mix CD4 and gp120 together. The intramolecular interacting complex of the present invention formed between the virus coat peptide (gp120) and viral receptor peptide (CD4) is due to a natural attraction. The relevant data comes from thermodynamic analysis and the crystal structure of the gp120-CD4 complex. Thermodynamic studies indicate that free gp120 is a disordered molecule that continually "samples" conformations in solution. CD4 binding "induces" a more ordered gp120 conformation. The interaction between gp120 and CD4 involves main-chain and side chain atoms. The "hot spot" on gp120 is a deep, roughly spherical pocket that accommodates phe 43 in the CD4 CDR2 loop. The pocket is lined with highly conserved residues. Direct interatomic contacts between CD4 and gp120 involve some CD4 residues and 26 gp120 residues. These interatomic contacts include approximately 219 Van der Waals contacts and 12 hydrogen bonds. The Phe 43 (on CD4) engages in hydrophobic interactions with a glu, trp, gly and ile in the gp120 pocket as does a CD4 arg with a gp120 val. The intramolecular interacting complex formed between the gp120 and CD4 peptides linked by a foldable amino acid spacer is due to natural affinity. Thus, one skilled in the art would understand that the covalent complexes formed in the DeVico '723 and '454 references are not the same as the intramolecular interacting complexes of the present invention that are formed through natural attraction without the use of a chemical crosslinker.

Clearly, the covalently bonded complexes of both of the cited references are different from the chimeras of the present invention for numerous reasons. Specifically, the process of crosslinking with the crosslinking agent occludes certain epitopes that are exposed in the presently claimed chimeras. Further, the covalently bonded complexes of DeVico '723 and '454 formed by a crosslinking agent were able to withstand the harsh denaturing environment of SDS PAGE while complexes formed through affinity binding are not able to withstand such conditions. Still further, the chimeras of the

present invention are a single chain polypeptide that includes both the viral protein and the receptor protein in a single chain and separated from each other by an amino acid spacer, and thus, peptide bonds are formed in the entire **single chain polypeptide chimera**. Neither of the cited references, DeVico '723 or '454, teach or suggest a **single chain polypeptide chimera**.

According to the Office, the Chackerian, et al. reference was cited for the "mere showing that making chimeras between a virus receptor and a virus coat has been done in the past." However, the Office must recognize that the Chackerian, at al. chimeras do not include chimeras wherein the virus coat polypeptide sequence and the viral receptor polypeptide sequence have a bonding affinity for each other as in the presently claimed invention. Instead the virus coat peptide was from bovine papillomavirus type 1 and the viral receptor peptide was from mouse CCR5. Clearly, the components described in the Chackerian, et al chimera are not capable of forming an interacting molecular complex via a natural attraction and in fact do not have any ligand-receptor capability. Thus the chimeras of Chackerian, et al., even when combined with the teachings of DeVico '723 or '454 do not teach or suggest the chimeras all of the elements of the presently claimed invention.

According to the Office:

> "The term 'intramolecular interacting complex' is not defined in the specification; the ordinary meaning of the term intramolecular interaction is the interaction a polypeptide chain experiences from the molecules in the chain."

Applicants agree that the intramolecular interacting complex is formed when peptides in the chain that are linked by the spacer interact. It is important to remember that applicants are discussing a **polypeptide chain that includes a linear sequence of peptide bonds that can form this intramolecular interacting complex through natural affinity.** When this intramolecular complex is formed the viral coat and viral receptor peptides are still connected through the amino acid spacer and in addition form the affinity bonding complex as discussed by Dr. DeVico in his declaration. The polypeptide chain is the important term in the claim because the polypeptide chain remains during this intramolecular interacting complex formation.

The Office speculates on DeVico '723 and '454 that "upon covalently bonding the two molecules any bonding and attractions they may have will then be termed intramolecular because once covalently bonded the complex as claimed in the DeVico '723 and '454 becomes a single molecule." However,

this statement contradicts the Office's earlier stated ordinary meaning of the term, which is the "interaction a **polypeptide chain** experiences from the **molecules in the chain**." (emphasis added) The Office seems to be giving a new meaning to the term "intramolecular interaction" when used in attempting to explain the covalent complexes of DeVico '723 and '454 that far extends beyond the ordinary meaning. Even if the chemically covalently bonded complexes of DeVico '723 and '454 become a single molecule, it does not mean they miraculously become a polypeptide chain. The DeVico '723 and '454 covalently bonded complexes are linked by a chemical crosslinker that binds only to amino ends of soluble peptides and this type of linkage does not provide for a polypeptide chain of continuous peptide bonds such as in the presently claimed invention. Clearly, the covalently bonded complexes of DeVico '723 and '454 are not connected through an amino acid spacer and thus **there is no interaction that a polypeptide chain experiences from the molecules in the chain**. If the Office has used the ordinary meaning of the term "intramolecular interaction complex" to mean an interaction that a polypeptide chain experiences from the molecules in the chain, then the meaning of the term must be consistent when used in light of the covalently bonded complexes of DeVico '723 and '454.

In respect of the Office's unsupported assertion that "upon covalently bonding the two molecules any bonding and attractions they may have will then be termed intramolecular because once covalently bonded the complex as claimed in the DeVico '723 and '454 becomes a single molecule," applicants hereby require an affidavit of the Examiner under the provisions of 37 CFR §1.104 ("Nature of examination"), which states in paragraph (c)(2) that

> **"[i]n rejecting claims for want of novelty or for obviousness, the examiner must cite the best references at his or her command"**

and in paragraph (d)(2) requires that

> **"[w]hen a rejection in an application is based on facts within the personal knowledge of an employee of the Office, the data shall be as specific as possible, and the reference must be supported, when called for by the applicant, by the affidavit of the employee, and such affidavit shall be subject to contradiction or explanation by the affidavits of the applicant and other persons."** (emphasis added)

Applicants therefore call for the examiner's affidavit specifically supporting the Examiner's statement that "upon covalently bonding the two molecules any bonding and attractions they may have will then be termed intramolecular because once covalently bonded the complex as claimed in the DeVico '723 and '454 becomes a single molecule."

This call for the Examiner's affidavit is based on the fact that **applicants are unaware of any references or knowledge in the field of chemistry that support the Examiner's contention of** "upon covalently bonding the two molecules any bonding and attractions they may have will then be termed intramolecular because once covalently bonded the complex as claimed in the DeVico '723 and '454 becomes a single molecule."

The applicants therefore assert that there is in fact no *prima facie* case of obviousness, since the combination of DeVico '723 or '454 in view of Chackerian, et al. is fundamentally deficient in teaching or suggestion of applicants' claimed invention. Applicants respectfully request withdrawal of all rejection under claims 1-8, 10, 11 and 73 were rejected under the judicially created doctrine of obviousness-type double patenting and U.S.C. §103(a).

Replacement Declaration and Power of Attorney

Applicants include herewith a replacement Declaration and Power of Attorney which makes reference to the priority claim to U.S. Provisional Application No. 60/158,321. Applicants request that the Declaration filed on April 20, 2001 be replaced with the newly executed Declaration included herewith. (Appendix B)

Petition for Extension of Time/Fees Payable

The applicants hereby petition for a three (3) month extension of time, extending the deadline for responding to the July 14, 2003 Office Action from October 14, 2003 to January 14, 2004. The entry of this petition results in a petition fee of $475.00.

The total fee of $860.00 is authorized to be charged in the attached credit card authorization form, which includes the petition fee for a three-month extension and the filing fee for a Request for Continued Examination. Authorization also is hereby given to charge any deficiency in applicable fees for this response to Deposit Account Number 08-3284 of Intellectual Property/Technology Law.

Conclusion

Applicants have satisfied all the requirements for patentability. All pending claims are free of the art and fully comply with the requirements of 35 U.S.C. §112. It therefore is requested that Examiner Winkler reconsider the patentability of claims 1-3, 6-11, 13-16, 24 and 73 in light of the distinguishing remarks herein and withdraw all rejections, thereby placing the application in condition for allowance. Notice of the same is earnestly solicited. In the event that any issues remain, Examiner Winkler is requested to contact the undersigned attorney at (919) 419-9350 to resolve same.

Respectfully submitted,

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